UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARTIN BILLGER, and MIKAEL BRULLS

Appeal No. 2004-1216
Application No. 09/674,002

HEARD: JULY 13, 2004

Before WINTERS, ADAMS, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-7, 9, 12, 17, 18, 20-28 and 31-36.[1] Claim 1 is representative of the subject matter of the appeal and reads as follows:

1. A stable, liquid pharmaceutical formulation of human parathyroid hormone at a concentration of 0.3 mg/ml to 10 mg/ml, comprising (i) human parathyroid hormone, (ii) a pharmaceutically acceptable buffer of pH 4 to 6 (iii) NaCl, (iv) mannitol, (v) a preservative, and (vi) water.

The examiner relies upon the following references:

Holthuis et al. (Holthuis)	5,496,801	Mar. 05, 1996
Selsted	5,547,939	Aug. 20, 1996
Endo et al. (Endo)	5,563,122	Oct. 08, 1996

[1] Claims 29 and 30 stand withdrawn from consideration, as being drawn to a non-elected invention.

Claims 1-7, 9, 12, 17, 18, 21-24, 26-28 and 31-36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Holthuis and Endo et al. Claims 20 and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Holthuis and Endo as further combined with Selsted. After careful review of the record and consideration of the issues before us, we affirm both rejections.

BACKGROUND

"Human parathyroid hormone (PTH) is an 84 amino acid protein involved in calcium and phosphorus homeostasis and control of bone growth and density." Specification, page 1. "Human PTH may be obtained through tissue extraction, from peptide synthesis or from genetically engineered yeast, bacterial or mammalian cell hosts." Id. PTH may be used in the treatment of osteoporosis. See id.

The specification notes that increasing the concentration of many proteins increases their propensity to aggregate and precipitate, which is highly undesirable for the formulation of pharmaceutical preparations. See id. at 2. PTH, according to the specification, is a protein that is prone to aggregation when the concentration is increased. See id. Strategies that have been used to compensate for the aggregation include changing the pH of the solution, and increasing the dosage volume. See id. The specification also teaches that PTH is also particularly sensitive to various forms of degradation, and that the degradation reactions may lead to partial or complete loss of

PTH bioactivity. See id. at 2-3. The disclosed invention is thus drawn to a pharmaceutical formulation containing a relatively high concentration of PTH formulation in a liquid form that may be lyophilized and reconstituted prior to either single or multiple administrations. See id. at 4.

DISCUSSION

The examiner rejects claims 1-7, 9, 12, 17, 18, 21-24, 26-28 and 31-36 under 35 U.S.C. §103(a) as being obvious over Holthuis in view of Endo. See Examiner's Answer, page 3. As the claims stand or fall together, see Appeal Brief, page 2, we focus our analysis on the broadest claim, i.e., claim 1.

Holthuis is cited by the rejection for teaching "a pharmaceutical formulation comprising human parathyroid hormone (1-84), mannitol as an excipient, and citrate as buffering agent in both lyophilized and liquid form and a method for treating a bone related disorder, osteoporosis using the formulation." Examiner's Answer, page 3. Holthuis, according to the rejection, specifically teaches a PTH formulation comprising 0.09 mg/ml to 2.27 mg/ml human PTH, 50 mg/ml of mannitol, and 10mM citrate buffer at a pH between 4 and 6, wherein the formulation was prepared in liquid form and then lyophilized. See id. at 4. Holthuis further teaches the benefits of the use of a bacteriostatic agent during reconstitution, and teaches that the reconstituted protein may be refrigerated for subsequent use in the next several days. See id. The rejection acknowledges "Holthuis [ ] fail[s] to explicitly teach inclusion of sodium chloride (NaCl) in their pharmaceutical formulation." Id.

Endo is cited for teaching "that addition of sodium chloride, in the presence of mannitol, further stabilizes PTH," and for teaching "that distilled water, physiological saline (aqueous solution of NaCl) or buffer solutions can be used to reconstitute the lyophilized composition containing PTH." See id. at 4. The rejection concludes:

> Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute the dried composition comprising PTH taught by Holthuis [ ] with saline, which would yield a stable, liquid pharmaceutical composition comprising NaCl, with a reasonable expectation of success. One would have been motivated to do so because saline is one of the most commonly used pharmaceutically acceptable carriers, as taught by Endo [ ] and Holthuis [ ].
>
> It would also have been obvious to one having ordinary skill in the art at the time the invention was made to include NaCl in the dried PTH formulation of Holthuis [ ], with a reasonable expectation of success. One would have been motivated to do so because Endo [ ] demonstrate[s] that addition of sodium chloride, in addition to mannitol further stabilizes PTH . . . . Reconstitution of the dried PTH formulation comprising NaCl with distilled water would yield a liquid pharmaceutical formulation comprising PTH and NaCl, which clearly reads on the instant claims.

Id. at 4-5.

"[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citation omitted). An adequate showing of motivation to combine requires "evidence that 'a skilled artisan, confronted with the same problems as the

inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000). We agree with the examiner that the combination of the references renders the composition of claim 1 obvious.

Appellants argue that the prior art does not teach a stable, liquid, human parathyroid hormone formulation. See Appeal Brief, page 5. Endo, according to appellants, added sodium chloride and mannitol to produce a stable lyophilized formulation. See id. Appellants contend that "there is no suggestion from Holthuis or Endo to generalize from a lyophilized to a liquefied parathyroid hormone formulation that can be stored for months at a time, and nothing in the prior art predicted or suggested Appellants' unexpected results." Id.

Claim 1 is drawn to "[a] stable, liquid pharmaceutical formulation of parathyroid hormone." As noted by the rejection, while both Holthuis and Endo pertain to lyophilized parathyroid hormone preparations, each reference teaches reconstitution of the lyophilized preparation into a liquid preparation before administration. Thus, the combination clearly teaches a liquid pharmaceutical formulation.

The issue thus narrows down to the use of "stable" in the claims. First, we note that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. See In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Nowhere in the

disclosure as filed, however, do the appellants tender a meaning for the term "stable." The specification discloses Tables examining the stability of different formulations, see Specification, pages 13-17, but the Tables all start at a time line of 0 days. See Specification, pages 13-17. We thus interpret "stable" to encompass the two to three days from reconstitution to administration as taught by Holthuis, and therefore find that the combination does teach a stable, liquid pharmaceutical formulation having the recited components.

Appellants argue further that the examiner failed to recognize the state of the prior art, in that it contravened conventional wisdom to incorporate sodium chloride into a highly concentrated parathyroid hormone formulation. See Appeal Brief, page 6. The appellants point out that Holthuis references "Martindale: The Extra Pharmacopoeia," which teaches away from incorporating PTH into a NaCl solution. See Id. at 7. According to appellants that reference teaches away from the claimed invention by teaching that "[s]oduim chloride solutions should not be used as they often cause precipitation." See Martindale: The Extra Pharmacopoeia, page 1338, The Pharmaceutical Press, London, 29th Ed., 1989. Appellant argues that Martindale is a general teaching relating reliable and unbiased information. See Reply Brief, page 2. The Martindale reference relied upon by appellants, however, was published in 1989, well before appellants' December 27, 2000 filing date. An updated version of the Martindale reference published in 1996, and thus more pertinent to the state of the art at the time of filing, fails to include the warning on precipitation. See Martindale: The

Extra Pharmacopoeia, page 742, Royal Pharmaceutical Society, London, 31st Ed., 1996. Thus we do not agree with appellants that the 1989 Martindale reference is sufficient evidence to rebut the prima facie case of obviousness given the lack of warning in the later Martindale, as well as the explicit teaching of Endo that addition of sodium chloride, in the presence of mannitol, further stabilizes parathyroid hormone formulations.

Appellants also cite CA 2,234,724 to support the assertion that the state of the art taught away from the use of sodium chloride in parathyroid hormone preparations. That reference, according to appellants, teaches that "sodium chloride 'favours the formation of dimers,' which are 'problematic in pharmaceutical forms of administration since they can lead to undesired side-effects when administered to patients due to immunological reactions.'" Appeal Brief, page 7. The reference is also cited by appellants for it's teaching that dimerization could lead to a loss of activity when stored over a long time. See id.

Again, we do not find that the teachings of the CA 2,234,724 reference as relied upon by appellants are sufficient to rebut the prima facie case of obviousness. Endo specifically encourages the use of sodium chloride, in combination with mannitol, as a method of stabilizing parathyroid formulations for long term storage, which contravenes the teachings of the CA 2,234,724 reference, relied upon by appellants. "When prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill." In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (1991). Because Endo was able to achieve the

results the CA 2,234,724 reference cautions against, and as Endo relates to the use of sodium chloride and mannitol, as required by claim 1, whereas the CA 2,234,724 reference in Table I looks at the combination of sodium chloride and sucrose, Endo is considered a better reflection of the current state of the art.

With respect to the rejection of claims 20 and 25 over the combination of Holthuis and Endo as further combined with Selsted, Appellants argue that the antimicrobial agent in Selsted is a tryptophan –rich indolicidin protein analog, and not EDTA alone. See Reply Brief, page 4. Thus, appellants contend that "[a]t the very most, the skilled artisan would likely have been motivated to add indolicidin and EDTA to Holthuis' or Endo's PTH formulation, but would not have been motivated to add EDTA alone. Id. (emphasis in original). That argument is not convincing, however, as the use of the term "comprising" in the claims leaves the claims open to the addition of additional components, such as indolicidin, and the rejection is affirmed.

CONCLUSION

For the reasons stated above, the rejection of claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 under 35 U.S.C. §103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Sherman D. Winters)
Administrative Patent Judge)
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Donald E. Adams) BOARD OF PATENT
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